a membrane. Both of these parameters can affect membrane protein function. Studies in our lab have shown that single hydrophilic residues within a hydrophobic sequence can have a profound effect upon both stability of the TM configuration and TM helix transverse position, such that a non-TM topography, or a shifted state in which the hydrophilic residues moves to the boundary of the membrane, respectively, forms. We have also found that the composition of membrane lipids can control topography. Most strikingly, physiologic levels of anionic lipids stabilize the TM configuration of hydrophobic helices that are flanked by cationic juxtamembrane residues, but not when the helices are flanked by uncharged residues. Interestingly, the effects of the lipids PS and PG are not identical, suggesting that factors in addition to Coulombic electrostatic interactions are involved. Our most recent studies indicate that anionic lipids can also effect the transverse position of hydrophobic helices. When a helix is flanked by cationic residues, the presence of anionic lipids suppresses the transverse TM helix shifts induced by hydrophilic residues within a hydrophobic helix. These studies show that anionic lipids can have significant and headgroup structure-specific effects upon membrane protein topography.

7-Subg
Control of Membrane Remodeling at the Golgi Through Sensors of Membrane Curvature: The ALPS Motif
Bruno Antonny[1], Joelle Bigay[1], Jean-François Casella[1], Guillaume Drin[1], Bruno Mesmin[1], Vincent Morello[1], Pierre Gounon[2], Romain Gautier[1].
[1]Institut de Pharmacologie Moleculaire et Cellulaire CNRS, VALBONNE, France, [2]Université de Nice Sophia Antipolis, Nice, France.
During the formation of coated vesicles the curvature of the lipid membrane strongly increases. This change can be sensed by specific motifs named ALPS that are present in some regulators of COP vesicles. ALPS motifs are intrinsically unstructured but fold as amphipathic helices at the surface of curved lipid membranes (radius < 50 nm). The sharp response to membrane curvature relies on the atypical polar face of the helix. Made mostly by Ser, Thr and Gly residues, this face cannot contribute to membrane binding. Thus membrane adsorption relies mostly on the insertion of the hydrophobic residues, which is favored by the lipid packing defects induced by membrane curvature. Two examples will be described where ALPS motifs permit to organize in time and in space reactions at the surface of membranes. The first example is the disassembly of the COPI coat. The lifetime of a coat must be finely tuned such as to be compatible with the capture of cargo and with membrane remodeling (budding, fission). We have identified two ALPS motifs in ArfGAP1, which controls COPI disassembly by catalyzing GTP hydrolysis in Arf1, one component of this coat. The remarkable sensitivity of ArfGAP1 to membrane curvature suggests that Arf1-GTP molecules are gradually eliminated from the center of the coat but not at the periphery during membrane budding. The second example is the tethering of transport vesicles by the long coiled-coil protein GMAP-210. We demonstrate that GMAP-210 can bridge small vesicles through its N-terminal ALPS motif to membranes primed with Arf1-GTP through its C-terminal GRAB domain. Interestingly, ArfGAP1 can disrupt this interaction when membrane curvature increases. This suggests that GMAP-210 acts as a molecular vector connecting in an asymmetric and reversible manner flat and curved membranes.

8-Subg
From Hydrophobic Matching to Interfacial Tuning: New Ideas for the Mutual Adaptation Between Membranes and Peptides
Jesús Salgado.
University of Valencia, Paterna (Valencia), Spain.
It is widely accepted that membrane proteins and lipid bilayers are complementary in terms of the distribution in space of their hydrophobic and polar regions. Similarly, it is also accepted that the hydrophobic parts of the protein and the membrane must adapt to each other. Classically these ideas are rationalized under the concept of hydrophobic matching, which predicts a number of possible mechanisms by which proteins can vary their effective hydrophobic length, or membranes can change their hydrophobic thickness. Such effects have been studied in detail for simplified systems, like transmembrane peptides or protein fragments, which generally show that optimizing peptide orientation is the principal adaptation response.
Based on simple computational methods, we show that the relative positioning, including orientation, of a peptide in a membrane can be easily and accurately predicted if the bilayer interfaces are taken into account. This allows studying in detail the adaptations of peptides to membranes, showing that, together with the classical coarse adjustment achieved by changes of the peptide tilt, there can be fine tuned adjustments through the azimuthal rotation. The latter tuning effect occurs mainly by optimizing positions of residues near the interface, and because it involves small changes of free energy, it provides a mechanism for high peptide dynamics. Additionally it strengthens the importance of the bilayer interface for the mutual adaptation of membranes and proteins and gives a new framework for the definition of so called flanking (or anchoring) residues.

Subgroup: Permeation & Transport

9-Subg
Coupling and uncoupling of Cl− and H+ movements through CLC transporters and channels
Christopher Miller.
Brandeis Univ, HHMI, Waltham, MA, USA.

10-Subg
Mechanism of Ion Recognition by Over-coordination: "The Caress of the Surroundings"[1]
Sameer Varma, **Susan Rempe**.
Sandia National Laboratories, Albuquerque, NM, USA.
Transferring Na^+ and K^+ ions from their preferred coordination states in water to states having different coordination numbers incurs a free energy cost. In several examples in nature, however, these ions *readily* partition from aqueous-phase coordinations into spatial regions having much higher coordination numbers. In particular, crystallographic data for the celebrated potassium channels show that their binding sites coordinate K^+ using eight carbonyl ligands, all within 3.0 Å from K^+. This makes for twice as many ligands as seen preferentially around K^+ in aqueous phase,[2,3] which would seemingly suggest an enormous uphill transition on the free energy surface.
We combine quantum, classical, and structural informatics studies to interrogate ion partitioning from low coordinations in water to over-coordinated[4,5] binding sites in proteins. Our results define the important role of the ligand surroundings in driving transitions in ion coordination structure, which underlies ion recognition in some proteins like potassium channels.[6]
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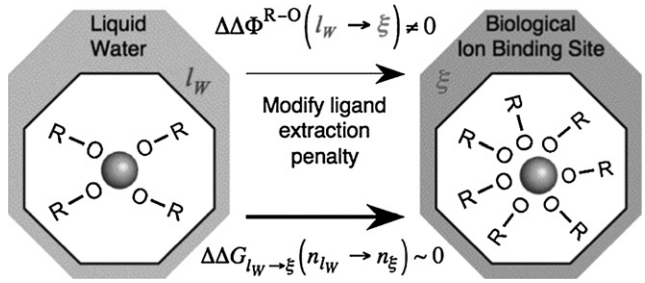

11-Subg
CTR Structure and Mechanism
Christopher J. De Feo[1], Stephen G. Aller[2], Yariv Barkan[3], Maya Shcushan[3], Gnana Siluvai[4], Nir Ben-Tal[3], Ninian J. Blackburn[4], **Vinzenz M. Unger**[1].
[1]Yale University, New Haven, CT, USA, [2]The Scripps Research Institute, La Jolla, CA, USA, [3]Tel-Aviv University, Tel-Aviv, Israel, [4]Oregon Health and Sciences University, Beaverton, OR, USA.
Copper uptake proteins (CTRs), mediate cellular acquisition of the essential metal copper in all eukaryotes. Using electron cryomicroscopy, we determined a 3D-structure of hCTR1 at ~7A resolution. The structure suggests that CTR1 proteins transport copper through a movement of Cu(I)-ions between defined binding sites and that intracellular copper chaperones are capable of directly obtaining copper from CTR1. To test these ideas, we used EXAFS to determine copper binding sites in hCTR1. We find that trimeric hCTR1 can stably bind 2 Cu(I)-ions through 3-coordinate Cu-S bonds. Moreover, EXAFS data obtained using Se-Cys-labeled CCS is consistent with the idea that the chaperone can obtain Cu(I) directly from copper loaded hCTR1. Modeling of a hypothetical hCTR1-CCS complex furthermore suggests that CCS may be able to associate with the membrane. Such a partitioning would greatly increase the efficiency of copper transfer to the chaperone because it would allow CCS to find hCTR1 through a 2D-diffusional search rather than a 3D-random walk. In support of this idea, we find that hCCS can bind to bilayers in vitro. Lastly, we generated a C-alpha model of the membrane embedded region of hCTR1 to aid future mechanistic studies. The model is consistent with the results of an extensive Trp-scan analysis of the membrane domain of hCTR1 and yCTR3 in that the overwhelming majority of residues found to be structurally and/or functionally important participate in helix packing interactions or face the copper permeation pathway along the 3-fold axis the CTR trimer.